Use of Atosiban in a Twin Pregnancy With Extremely Preterm Premature Rupture in the Membrane of one Twin: A Case report and Literature Review

Ming-Yih Wu, Shee-Uan Chen, Chien-Nan Lee, Hong-Nerng Ho, Yu-Shih Yang*

Department of Obstetrics and Gynecology, College of Medicine and the Hospital, National Taiwan University, Taipei, Taiwan.

SUMMARY

Objective: Pregnancies with extremely preterm premature rupture of membranes (EPPROM), especially before 20 weeks of gestation, are usually considered to be a termination of pregnancy. By improvement of obstetric and neonatal care, we can prolong the pregnancy across the threshold of survival by aggressive tocolysis.

Case Report: Using intrauterine insemination, a 32-year-old woman became pregnant with twins (first pregnancy). Threatened abortion occured since 9 weeks of gestation and EPPROM of the upper twin was noted at 18 weeks. Massive vaginal bleeding and vigorous uterine contractions occurred at 22 weeks. Poor control of preterm labor occurred using ritodrine and $MgSO_4$. Atosiban was applied to calm uterine activities. After discontinuation of atosiban at 30 weeks, the uterine contractions became severe again and an emergency cesarean section was performed to deliver two live, premature babies weighing 1,518 g and 830 g, respectively. Twin A was healthy, weighing 2,030 g at 35 days after birth and subsequently discharged. The smaller twin B was dependent on continuous positive airway pressure and died of pulmonary infection 120 days after birth.

Conclusion: Comparing to other tocolytic agents, Atosiban has few side effects and assisted in prolonging a pregnancy involving twins that experienced EPPROM. [*Taiwan J Obstet Gynecol* 2010;49(4):495–499]

Key Words: atosiban, EPPROM, twin pregnancy

Introduction

Preterm premature rupture of membranes (PPROM) is a complication in approximately one-third of all preterm deliveries, and involves a high risk of fetal and maternal morbidity [1]. Among twins with PPROM, approximately 6% were stillbirths, 15% were neonatal deaths and 14% were reported as infant mortality, in the United States [2]. Those twins with extremely preterm premature rupture of membranes (EPPROM) prior to 20 weeks exhibited worse results. Assisted reproduction technology (ART) for infertile couples is strongly associated with twinning and twins remain a high-risk group compared with singletons [3]. Among people having difficulty conceiving, prolongation of twin pregnancies was more frequently claimed. We have previously obtained some twins with EPPROM of the upper [4] or lower sac [5].

The most common tocolytic agents used in preterm labor are ritodrine (Yutopar) and magnesium sulfate ($MgSO_4$). However, betamimetics like ritodrine are significantly associated with palpitations, nausea, tremor, chorioamnionitis, hyperglycemia and hypokalemia [6], therefore treatment needs to be discontinued. A recent double-blind trial of $MgSO_4$ used between 24 and 31 weeks failed to reduce the risk of cerebral palsy or death due to preterm delivery [7]. In addition, compromised respiration after $MgSO_4$ therapy for preterm labor was also a concern [8]. Recently, atosiban (Tractocile) was

*Correspondence to: Dr Yu-Shih Yang, Department of Obstetrics and Gynecology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: yangys@ntu.edu.tw
Accepted: January 13, 2009

introduced for delaying preterm delivery before the threshold of viability [9]. More recently, a randomized study in Korea [10] demonstrated that atosiban, a highly uterospecific tocolytic agent, was superior to ritodrine in both safety and efficacy.

Case Report

A 32-year-old woman achieved her first pregnancy (twins) by intrauterine insemination. Prior to this, she suffered from 2 years of infertility due to ovarian dysfunction, and an irregular menstrual cycle with mild hirsutism compatible with polycystic ovary syndrome. She also received a laparoscopic left oophorocystectomy for a chocolate cyst (6 × 5 × 5 cm). At 9^{+3} gestational weeks, she was admitted due to vaginal bleeding and pelvic cramps. Pelvic ultrasound revealed a subchorionic hematoma measuring 3.9 × 3.0 × 2.5 cm beneath twin B. Complete bed rest was prescribed and oral progesterone (Utrogestan) dosage was increased from 300 mg to 600 mg per day. She was discharged 5 days later, and the vaginal bleeding had stopped. The hematoma had grown to 7.1 × 4.8 × 6.1 cm at 12 weeks. The second trimester maternal serum screening returned the result of a high risk of Down's syndrome (1/84), and the patient was advised to undergo amniocentesis.

At 18 weeks and 1 day, amniocentesis was performed. The biparietal diameter (BPD) was measured as 4.0 cm of twin A (right lower, female), and 3.8 cm of twin B (left upper, male). The evening after amniocentesis, the patient felt apparent fluid leakage from the vagina. A follow up ultrasound revealed nearly no amniotic fluid for twin B, so iatrogenic EPPROM was documented. The results of chromosome and spinal muscular atrophy screening were normal. Fetal screening ultrasound performed at 19 weeks demonstrated anhydramnios of twin B. Repeated sonography at 21, 22, 23 weeks showed identical results. At 22 weeks and 5 days, she visited our emergency department due to sudden onset of vaginal bleeding (hemoglobin = 10.0 g/dL). There were some blood clots and mucus from the cervix, with the cervix slightly effaced but not dilated. After discussion with the patient and her family about the risk and prognosis, they chose to allow the pregnancy to continue. Due to prolonged EPPROM for 2 more weeks, intravenous antibiotics (Cefa) were given despite low C-reactive protein (CRP) levels (0.8 mg/dL). When ritodrine was infused at a dosage of 8 mg per hour, the patient complained of severe palpitation and nausea but the uterine contractions were still active (3–5-minute intervals). Atosiban was added to control the preterm labor, and on the next day, $MgSO_4$ was added to attenuate the uterine contractions. The tocolytic agents were kept near the highest threshold: ritodrine 20.8 mg/hr, $MgSO_4$ 1.6 g/hr, atosiban 9 mg/hr. The CRP levels peaked at 4.68 mg/dL at 3 days post-admission and fluctuated thereafter. Cervical cultures were performed once or twice per week, and antibiotics changed according to results of drug sensitivity tests. Intermittent vaginal bleeding was also noted with anemia (hemoglobin = 8.3 gm/dL) at 23 weeks, but improved afterwards. Corticosteroids were given for lung maturation at 26 weeks. At 28 weeks, the fluid leakage stopped for 5 days and amniotic fluid reappeared in twin B, at a depth of 2.0 cm. The family asked to discontinue atosiban treatment due to its high cost. One day later, uterine contractions increased, and fluid leakage combined with vaginal bleeding relapsed. Therefore, atosiban was restored again and the dose adjusted to 10.5 mg/hr for 2 days, and then back to 9 mg/hr. At 30 weeks, the family asked to taper the dose of atosiban to 6 mg/hr, once again due to its high cost. After that, uterine contractions reinforced and large vaginal blood clots followed. The patient complained of left lower abdominal pain and ultrasound showed blood accumulation behind twin B. An emergency Cesarean section performed done at 30 weeks and 2 days. Twin A had a birth weight of 1,518 g with an Apgar score of 8 and 9 at 1 and 5 minutes, respectively. Twin B weighed 830 gm only with Apgar score 1, 6 and 8 at 1, 5 and 10 minutes respectively. The cord of twin B was very small, and meconium stained chronically. There were fresh and old blood clots occupying one third of the placental base. Partial abruptio placenta was impressed but no fetal distress noted before delivery.

The CRP level in both twins was normal when checked at the neonatal intensive care unit but prophylactic antibiotics were given. Both twins were found with patent ductus arteriosus and recovered after two doses of indocin (0.2 mg/kg). Initially, both twins received nasal continuous positive airway pressure (CPAP) for ventilation support. Twin A recovered well and was removed from ventilation support 6 days later and was discharged 35 days after birth with a body weight of 2,030 gm.

Twin B suffered severe intrauterine growth retardation and respiratory distress. His lung condition was treated with high frequency oscillatory ventilation and on the second day, inhaled nitric oxide was given. A chest tube for left side pneumothorax was used on the third day and extubated 9 days later. Hemivertebrae at T7-T8 and T12 was also coincidentally noted. Brain sonography showed intraventricular hemorrhage grade II initially on the left side, and then persistent bilateral grade I periventricular echogenicities noted. Persistent CPAP dependence was noted and he started coughing

Table. Assisted reproduction technology-derived twins with one extremely preterm premature rupture of membrane before before 20 weeks of gestation

Author (year)	GA at PPROM (wk)	Method of conception	Procedures after PPROM	PPROM to birth (d)	GA at delivery (wk)	Twin A (g)	Twin B (g)
Borenstein & Shoham [17] (1990)	15	COH	–	119	32	1,100	1,500*
Wu et al [4] (1996)	19	COH	–	64	28^{+1}	1,166	1,116*
Chang et al [5] (1996)	18	AID	Cerclage	72	28^{+2}	NA*	1,232
Abboud et al [18] (1997)	17^{+1}	AIH	Cerclage	71	27^{+2}	NA*	1,070
Bakos et al [19] (1998)	13^{+5}	COH	–	100	28	455*	1,270
Jazayeri et al [20] (2002)	17	IVF	Cerclage	105	32	NA*	2,070
Hamersley et al [21] (2002)	15^{+2}	ART	Cerclage	153	37^{+1}	NA*	2,863
	18^{+4}	ART	Cerclage	23	22	NA*	NA
Keselman et al [22] (2008)	16	AIH	Fetocide + Cerclage	140	36	NA*	2,500
	19	COH	Fetocide + Cerclage	119	36	2,500	NA*
Present case	18^{+1}	AIH	–	85	30^{+2}	1,518	830*

**The twin of EPPROM. AID = artificial insemination of donor; AIH = artificial insemination of husband; ART = assisted reproductive technology; COH = controlled ovarian hyperstimulation; EPPROM = extremely preterm premature rupture of membrane; GA = gestational age; IVF = in vitro fertilization; NA = not available; PPROM = preterm premature rupture of membrane.*

111 days after birth. Sputum virus isolation demonstrated parainfluenza type 3 infection. He had progressive dependence on oxygen and we used high-setting nasal intermittent positive pressure ventilation. His respiratory distress deteriorated thereafter and he died 120 days after birth.

Discussion

First-trimester bleeding is frequent in over 30% of ART pregnancies, and ultimately approximately half of them miscarry [11]. It is unknown whether first-trimester bleeding, if it does not end in a spontaneous abortion, negatively influences further pregnancy outcomes in ART. First-trimester bleeding has been shown to lead to increased second- and third-trimester bleeding rates, PPROM, and extreme preterm birth [11]. In this case, vaginal bleeding and sub-chorionic hematoma was detected at 9 weeks of gestation. Polycystic ovary syndrome in this patient may be another contributing factor of threatened abortion [12]. Prior to formation of large subchorionic hematoma, uterine contractions or so-called "myometrial thickenings" [13] supposedly occurred earlier but we have no evidence of this from her history.

Until recently, the treatment policy involved in patients of EPPROM before 20 weeks was usually termination of the pregnancy due to risk to both the mother and the fetus. Patients and doctors should devote more attention to those pregnancies which are difficult to achieve by ART. Most reported survivals for EPPROM occur at more than 20 weeks [14–16]. Through improvements in obstetrical and neonatal care, we have successfully delayed the preterm delivery of ART twins with EPPROM (Table) [4,5,17–22].

EPPROM in twins is more difficult to treat than EPPROM in singletons; therefore selective fetocide of the affected twin is a new option to accelerate the process of leakage sealing [22]. This case was referred to our emergency service at 22 weeks and 5 days of gestation, 32 days post-EPPROM. The EPPROM occurred in the upper twin sac, and we successfully handled the EPPROM of the lower twin sac [4]. After complete counseling with the patient and her family, we decided to attempt aggressive tocolysis to save both twins.

Unfortunately, traditional tocolytics such as ritodrine and $MgSO_4$ seemed unable to control her uterine activities after admission. Intolerable side effects like palpitation and hot flushes occurred very shortly after the use of ritodrine and $MgSO_4$, even at moderate doses. For that reason, the addition of atosiban was suggested. Atosiban has been shown to be an effective tocolytic agent with a low rate of side effects from 24 to 33 weeks of gestation. It has been introduced for use in intact membranes [23], PROM [24], or prior to cervical cerclage [25]. However, in a recent meta-analysis of six trials involving 1,695 women, the atosiban failed to reduce preterm birth, as compared with the placebo [26].

In a placebo-controlled trial [27] by Romero et al involving 531 subjects, 14 atosiban-treated patients and five placebo-treated patients were randomized at less than 24 weeks; the incidence of fetal-infant deaths was higher for the atosiban group at less than 24 weeks. However, in a recent prospective randomized study enrolling 40 women at less than 24 weeks gestation [28], atosiban was shown to be effective for tocolytic treatment of premature labor, even during weeks 18 and 24 of pregnancy.

The first and only agent approved for tocolysis by the US Food and Drug Administration was ritodrine. The approval of that drug in 1980 initiated a period of intense clinical exploration for other agents that might inhibit uterine contractions [29]. However, the side effects such as changes in maternal blood pressure, serum glucose levels and especially the subjective symptoms of palpitations lead to limited dosages of ritodrine [30]. $MgSO_4$ is another agent commonly used for tocolysis, with recent evidence showing elevated circulating levels of serum ionized magnesium occurring in mothers at the time of delivery associated with subsequent neonatal intraventricular hemorrhage [31]. Conversely, a more recent randomized controlled trial demonstrated that $MgSO_4$ given before very preterm birth would protect the infant brain and no major maternal adverse effects were observed [32]. However, monitoring the dosage, respiratory suppression, and hot flushes compromises the use of $MgSO_4$.

Deliveries at 20–25 weeks of gestation are associated with significant morbidity and mortality. If EPPROM were to occur before 20 weeks a poorer prognosis would be expected. In our case of twins with one experiencing EPPROM, limited use by ritodrine and $MgSO_4$ made tocolysis more difficult because of side effects. Atosiban has been shown to be beneficial in prolonging the pregnancy of spontaneous labor at very early gestational periods [9]. Applied even during weeks 18 and 24, atosiban is also effective for tocolytic treatment for preterm labor with a favorable profile of side effects [28]. Therefore, we added atosiban combined with ritodrine and $MgSO_4$ to control the preterm labor. One of the major concerns of atosiban in Taiwan is its high cost, for those pregnancies from ART or twins, it is more economically acceptable.

One of the major neonatal outcomes of EPPROM is pulmonary hypoplasia, which occurs in 60% of pregnancies at 14–19 weeks of gestation, 13% at 20–25 weeks, and 0% at 26–28 weeks in a Sweden study [33]. EPPROM in our case occurred in the upper twin sac, where it should have been easy to stop leakage [17]. Indeed, we found amniotic fluid accumulation at 26 weeks, but leakage occurred again. Twin B had severe intrauterine growth retardation but no evidence of infection, and was dependent on CPAP for a prolonged period, but eventually died of pneumonia 4 months later. His death may be attributable to pulmonary hypoplasia from EPPROM. Thus selective fetocide of the affective twin may be a reasonable choice under these conditions [22].

EPPROM occurring at 14–19 weeks, 20–25 weeks, and 26–28 weeks has perinatal survival rates of 40%, 92% and 100%, respectively [33]. In twins with one EPPROM, the distension of the uterus may lead to a poor prognosis. In addition to traditional tocolytic agents, atosiban with fewer side effects may be helpful for prolongation of those pregnancies with EPPROM.

References

1. Parry S, Strauss JF, III. Premature rupture of the fetal membranes. *N Engl J Med* 1998;338:663–70.
2. Kristensen S, Salihu HM, Ding H, Alexander GR. Early mortality in twin pregnancies complicated by premature rupture of membranes in the United States. *J Obstet Gynaecol* 2004;24:233–8.
3. Boulet SL, Schieve LA, Nannini A, et al. Perinatal outcomes of twin births conceived using assisted reproduction technology: a population-based study. *Hum Reprod* 2008;23:1941–8.
4. Wu MY, Yang YS, Huang SC, Ho HN. Prolongation of pregnancy and survival of both twins after preterm premature rupture of membrane of twin A and 19 weeks' gestation. *Acta Obstet Gynecol Scand* 1996;75:299–302.
5. Chang HC, Wu MY, Ho HN, Yang YS. Delayed delivery of surviving triplet after fetal reduction and spontaneous abortion. *J Formos Med Assoc* 1996;95:881–4.
6. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. *Obstet Gynecol* 1999; 94:869–77.
7. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008;359:895–905.
8. Catanzarite V, Gambling D, Bird LM, Honold J, Perkins E. Respiratory compromise after $MgSO_4$ therapy for preterm labor in a woman with myotonic dystrophy: a case report. *J Reprod Med* 2008;53:220–2.
9. Eogan M, McKenna P. Delaying preterm delivery at the threshold of viability. *J Obstet Gynaecol* 2004;24:459–60.
10. Shim JY, Park YW, Yoon BH, et al. Multicentre, parallel group, randomised, single-blind study of the safety and efficacy of atosiban versus ritodrine in the treatment of acute preterm labour in Korean women. *BJOG* 2006;113:1228–34.
11. De Sutter P, Bontinck J, Schutysers V, Van der EJ, Gerris J, Dhont M. First-trimester bleeding and pregnancy outcome in singletons after assisted reproduction. *Hum Reprod* 2006;21:1907–11.
12. Cocksedge KA, Li TC, Saravelos SH, Metwally M. A reappraisal of the role of polycystic ovary syndrome in recurrent miscarriage. *Reprod Biomed Online* 2008;17:151–60.
13. Tadmor OP, Rabinowitz R, Diamant YZ. Ultrasonic demonstration of local myometrial thickening in early intrauterine pregnancy. *Ultrasound Obstet Gynecol* 1995;5:44–6.

14. Hadi HA, Hodson CA, Strickland D. Premature rupture of the membranes between 20 and 25 weeks' gestation: role of amniotic fluid volume in perinatal outcome. *Am J Obstet Gynecol* 1994;170:1139–44.
15. Dinsmoor MJ, Bachman R, Haney EI, Goldstein M, Mackendrick W. Outcomes after expectant management of extremely preterm premature rupture of the membranes. *Am J Obstet Gynecol* 2004;190:183–7.
16. Shumway JB, Al Malt A, Amon E, et al. Impact of oligohydramnios on maternal and perinatal outcomes of spontaneous premature rupture of the membranes at 18–28 weeks. *J Matern Fetal Med* 1999;8:20–3.
17. Borenstein R, Shoham Z. Premature rupture of the membranes in a single twin gestational sac. A case report. *J Reprod Med* 1990;35:270–1.
18. Abboud P, Gallais A, Janky E. Intentional delayed delivery in twin pregnancy. Two additional cases and literature review. *Eur J Obstet Gynecol Reprod Biol* 1997;75:139–43.
19. Bakos O, Cederholm M, Kieler H. Very prolonged membrane rupture and delayed delivery of the second twin. *Fetal Diagn Ther* 1998;13:147–9.
20. Jazayeri A, Mamlok V, Dorsett MM, Porter KB. Prolonged-interval delivery between the first and second twin. A case report. *J Reprod Med* 2002;47:167–9.
21. Hamersley SL, Coleman SK, Bergauer NK, Bartholomew LM, Pinckert TL. Delayed-interval delivery in twin pregnancies. *J Reprod Med* 2002;47:125–30.
22. Keselman L, Perlitz Y, Younis J, Ben Ami M. Nonconventional approach to twin pregnancies complicated by extremely preterm premature rupture of membranes of one twin. *Am J Perinatol* 2008;25:161–2.
23. Moutquin JM, Sherman D, Cohen H, et al. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000;182: 1191–9.
24. Helmer H, Brunbauer M, Rohrmeister K. Exploring the role of Tractocile in everyday clinical practice. *BJOG* 2003;110 (Suppl 20):113–5.
25. Locci M, Nazzaro G, Merenda A, et al. Atosiban vs ritodrine used prophylactically with cerclage in ICSI pregnancies to prevent pre-term birth in women identified as being at high risk on the basis of transvaginal ultrasound scan. *J Obstet Gynaecol* 2006;26:396–401.
26. Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Rev* 2005;CD004452.
27. Romero R, Sibai BM, Sanchez-Ramos L, et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000;182:1173–83.
28. Richter ON, Dorn C, van de Vondel P, Ulrich U, Schmolling J. Tocolysis with atosiban: experience in the management of premature labor before 24 weeks of pregnancy. *Arch Gynecol Obstet* 2005;272:26–30.
29. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007;357:477–87.
30. Chan J, Cabrol D, Ingemarsson I, Marsal K, Moutquin JM, Fisk NM. Pragmatic comparison of beta2-agonist side effects within the Worldwide Atosiban versus Beta Agonists study. *Eur J Obstet Gynecol Reprod Biol* 2006;128:135–41.
31. Mittendorf R, Dammann O, Lee KS. Brain lesions in newborns exposed to high-dose magnesium sulfate during preterm labor. *J Perinatol* 2006;26:57–63.
32. Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*. *BJOG* 2007;114:310–8.
33. Farooqi A, Holmgren PA, Engberg S, Serenius F. Survival and 2-year outcome with expectant management of second-trimester rupture of membranes. *Obstet Gynecol* 1998;92: 895–901.